ISBN 978-1-960740-14-4

NUTRITION AND DIETETICS - FUNDAMENTAL AND PRACTICAL CONCEPTS

Review Based Book Chapter

NUTRITIONAL DEFICIENCY DISORDERS AND SUPPLEMENTS

Publication Date
December 18, 2023
doi: 10.5281/zenodo.10411286

Scientific Knowledge Publisher (SciKnowPub), USA
info@sciknowpub.com

REVIEW BASED BOOK CHAPTER

NUTRITIONAL DEFICIENCY DISORDERS AND SUPPLEMENTS

Kunzul Kashif[1], Dua Naveed[1], Rameesha Azhar[1], Rabia Ali[1], Momina Asif[1], Saba Hasnain[1], Rabiatul Adawiyah Binti Umar[2], Umar Bacha[1], Shanthi Krishnasamy[3], Wan Rohani Wan Taib[2], Atif Amin Baig[4], Faheem Mustafa[1,2]

[1]Department of Nutrition and Dietetics, School of Health Sciences, University of Management and Technology, Lahore, Pakistan
[2]Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Malaysia
[3]Faculty of Health Sciences, National University of Malaysia
[4]International Medical School, Management and Science University, Malaysia

For Correspondence
faheem.mustafa@umt.edu.pk

Abstract

Micronutrient deficiencies refer to insufficiencies in essential vitamins and minerals required for optimal physiological function. These vital nutrients, including vitamins A, C, D, and minerals such as iron, zinc, and calcium, play a crucial role in supporting various bodily functions. Micronutrient deficiencies can arise due to inadequate dietary intake, dietary restrictions, or underlying medical conditions, and their repercussions extend far beyond dietary concerns, significantly impacting overall health. The link between micronutrient deficiencies and health outcomes is profound, influencing diverse aspects of well-being. This chapter explores the critical issue of nutritional deficiencies and highlights their significance in maintaining optimal health. It emphasizes the crucial role of a balanced diet and lifestyle adjustments in effectively addressing these deficiencies. By focusing on dietary patterns and maximizing nutrient intake through the consumption of balanced meals and appropriate supplementation, individuals can mitigate the adverse effects of nutritional deficiencies. However, challenges related to the affordability and accessibility of nutritious food persist, necessitating comprehensive government-led initiatives and nutrition education programs. The chapter delves into the various causes of nutritional deficiencies, including inadequate dietary intake and underlying medical conditions. It underscores the importance of addressing these deficiencies to prevent the onset of various health conditions and improve skeletal-muscular health. Additionally, the chapter discusses the potential interactions between medications and dietary supplements, emphasizing the need for caution and awareness. Overall, this chapter provides valuable insights into the significance of nutrition in maintaining optimal health and offers practical strategies to effectively address nutritional deficiencies.

Keywords *Nutritional Deficiencies, Balanced Diet, Lifestyle Adjustments, Dietary Patterns, Nutrient Intake, Supplementation, Nutrition Education*

1. Introduction to Nutritional Deficiencies

1.1. Brief overview of the importance of a balanced diet

A balanced diet includes both macro and micro-nutrients from the seven food groups. It has optimized proportions of carbohydrates, fats, and proteins. Utilizing complex carbs over simple carbs, avoid Tran's fats and saturated fats while relying on unsaturated fats. The inclusion of dietary fiber with the increase in vegetables and fruit servings, avoidance of additive sugars, and daily intake of the dairy group, all these practices together form a balanced diet. Calories gained from the diet fuel the body. A balanced diet ensures the availability of all the essential nutrients, vitamins, and minerals required for optimal functioning of our body. Without it, our body is prone to diseases infections, and fatigue [1].

One of the most important reasons for maintaining a balanced diet is to ensure that the body receives the necessary nutrients for energy and growth [2]. Carbohydrates, proteins, and fats are all essential macronutrients that the body needs to function properly. Carbohydrates are the body's main source of energy, while proteins are necessary for muscle and tissue growth and repair, and fats are important for various bodily functions, including hormone production and nutrient absorption. With a balanced diet that includes these macronutrients in the right proportions, the body may have the energy and the building blocks it needs to grow and thrive.

In addition to macronutrients, a balanced diet includes essential vitamins and minerals necessary for various bodily functions. For example, vitamin A is important for vision and immune function, vitamin C is important for collagen production and immune function, and calcium is important for bone health. Without these essential vitamins and minerals, the body may be at risk for various deficiencies and health problems.

Furthermore, a balanced diet is important for preventing and managing various health conditions [3]. For example, a diet high in fruits and vegetables, whole grains, and lean proteins can help reduce the risk of chronic diseases such as heart disease, diabetes, and certain types of cancer. On the other hand, a diet high in processed foods, sugar,

and unhealthy fats can increase the risk of these diseases. By maintaining a balanced diet, individuals can protect their overall health and well-being.

1.2. Definition and causes of nutritional deficiencies

Learners confuse two different yet similar terms when talking about nutritional deficiencies often. Mostly they are talking about nutritional inadequacy but coin that concept as nutritional deficiency. The term "Nutritional deficiency" refers to deficient levels of one or more nutrients that impede the body from completing its regular tasks and raise the risk of diseases such as diabetes, heart disease, and cancer. "Nutritional inadequacy" refers to taking fewer nutrients than the estimated average requirement [4].

Malnutrition can be caused by environmental factors such as food scarcity as well as medical issues such as anorexia nervosa, fasting, trouble swallowing, frequent vomiting, poor digestion, intestinal malabsorption, or other chronic disorders. Nutritional biomarkers, such as serum or plasma levels of nutrients like folate, vitamin C, B vitamins, vitamin D, selenium, copper, and zinc, can be used to assess nutrient intake and dietary exposure [5]. Macronutrient deficiencies can cause growth, ketosis, marasmus, and kwashiorkor.

1.3. Common Causes of Nutritional Deficiencies

To understand the causes of nutritional deficiencies, examining the factors contributing to inadequate dietary intake is crucial.

1.3.1. Inadequate dietary intake

Inadequate dietary intake is a major cause of nutritional deficiencies [6]. Many individuals do not consume a balanced diet that includes all the necessary nutrients. This can result from factors such as limited food availability, poverty, or personal choices also certain medical conditions. Research has shown that inadequate dietary intake is particularly prevalent in low- and middle-income countries, where poverty and limited access to nutritious foods play a significant role in causing nutritional deficiencies [2].

1.3.2. Limited food access and dysfunctional food systems

One of the main reasons behind nutritional deficiencies is a need for more access to a diverse and balanced diet. This is especially prevalent in low- and middle-income countries where poverty hinders individuals from obtaining sufficient quantities of essential nutrients. According to a study, an estimated 51% of preschool children suffer from one or several micronutrient deficiencies, highlighting the severity of the problem in these regions [7].

According to a study, dysfunctional food systems are a chief cause of malnutrition [8]. Malnutrition arises from dysfunctional food systems that fail to provide all the necessary nutrients for human sustenance. This results in deficient diets in vitamins, minerals, and other essential nutrients.

1.3.3. Poor absorption

Another common cause of nutritional deficiencies is poor absorption. Poor absorption occurs when the body is unable to effectively absorb or utilize nutrients from the diet. This condition is also known as Malabsorption [9]. This can be due to various factors such as gastrointestinal disorders, certain medications, or conditions that affect the absorption process in the intestines.

Several factors, such as damage to the intestine from infection, inflammation, trauma, or surgery can bring on malabsorption syndrome. Prolonged use of antibiotics, other conditions such as Crohn's disease, cystic fibrosis, chronic pancreatitis, or congenital abnormalities such as biliary atresia. Diseases of the gallbladder, liver, or pancreas; radiation therapy, or drugs that can damage the lining of the intestine. Research has shown that malabsorption can lead to deficiencies in nutrients like iron, vitamin B12, and calcium [9].

1.3.4. Increased nutrient requirements

Certain life stages or conditions may increase nutrient needs, leading to deficiencies if not met. Pregnancy and lactation are examples of life stages that require increased nutrient intake to support the growth and development of the fetus or newborn [10].

During pregnancy, the demand for nutrients such as iron, folate, and calcium significantly increases.

Medical conditions such as diabetes, thyroid disorders, and gastrointestinal diseases can also increase the body's nutrient requirements and potentially lead to deficiencies if not properly addressed and managed [11]. Research has shown that individuals with diabetes, for example, may have an increased risk of nutrient deficiencies such as vitamin B12, vitamin D, and magnesium.

1.3.5. Medical conditions

Certain medical conditions make it hard for patients or people to have an adequate nutritional intake and they also cause losses which lead to nutritional deficiencies. Conditions like dysphagia, sores, and ulcers in the oral cavity or esophagus make it hard to chew or swallow [12]. Similarly, stress, depression, sadness, and such mental illnesses as anorexia cause hindrance in the ability to nourish a person.

During critical illness, the body is in a hyper catabolic state in which muscle mass and energy stores are depleted and nutrients are used at a high rate. This catabolic state manifests clinically as weight loss, sarcopenia and undernutrition [13]. When the body is in a high catabolic state the nutritional losses are more compared to a normal body state. This high catabolic state occurs in chronic or acute medical conditions such as renal insufficiency, uncontrolled diabetes, and cancer.

1.3.6. Altered Metabolism

When the body's metabolism malfunctions and produces either an excess or deficiency of the vital substances required for good health, it is referred to as a metabolic disorder. A metabolic disorder may arise from malfunctions in any organ, such as the liver or pancreas. Genetics, a lack of a particular hormone or enzyme, eating too much of a particular food, or a combination of other factors can all contribute to these kinds of disorders. Mutations in individual genes give rise to hundreds of genetic metabolic disorders. Families may inherit these mutations from one generation to the next.

According to the National Institutes of Health (NIH), certain racial or ethnic groups are more likely to pass on mutated genes for specific inborn disorders [14].

1.3.7. Impact on Overall Health and Well-being

Micronutrient deficiencies can result in less clinically significant declines in energy level, mental clarity, and general capacity in addition to visible and dangerous health conditions. This may result in worse academic performance, less productivity at work, and a higher chance of contracting additional illnesses and ailments. A healthy diet rich in a variety of foods, nutrition education, and, when necessary, food fortification and supplementation can help avoid many of these deficiencies. Although these initiatives have significantly reduced micronutrient deficiencies in recent decades, more work is still required.

1.3.8. Skeleto-muscular health

Inadequate calcium and vitamin D can affect bone density, increasing the risk of fractures and osteoporosis. Increased risk for bone loss is linked to high intake of salt, low intake of calcium, and inadequate vitamin D. New research indicates that diet may also play other roles in bone loss. Calcium, essential for numerous vital body processes, is primarily stored in the bones. Calcium is taken up by the body from the bones if we do not get it from our food to absorb calcium, vitamin D is essential [15].

Inadequate nutrition can raise the risk of injury even in "active" and "healthy" individuals because it affects healing. A low dietary protein intake can cause muscle damage through several different pathways. Skeletal muscle deterioration resulting from intense training may be made worse by a low-protein diet. Insufficient fluid intake can disrupt the blood supply to active muscles, potentially elevating the risk of injury. Drinking enough water affects the quantity and makeup of joint fluid, which supports the development of articular cartilage. Due to the importance of these micronutrients in the metabolism of bone and muscle, deficiencies in potassium, iron, zinc, magnesium, chromium, copper, and other vitamins may make a person more vulnerable to injury [16].

1.3.9. Mental and emotional well-being

Inadequate nutrition can slow down response time, cause fatigue, and impair the ability of decision-making [17].

The synthesis of serotonin, dopamine, norepinephrine, and epinephrine depends on sufficient amounts of vitamin B-12 and folate. In cases of B-12 deficiency, mental illnesses such as dementia, psychosis, panic disorder, bipolar disorder, depression, and phobias may be identified. Decreases in vitamin B-12 and folic acid levels are correlated with elevated homocysteine in bipolar disorder patients. Absence of vitamin B6, thiamine (vitamin B1), and folic acid. A deficiency in these nutrients may lead to anemia, which can cause the person to become intolerant to cold, feel lethargic and lightheaded, and experience frequent headaches and dyspnea. Because it raises the risk of neurological disorders like Wernicke-Korsakoff Syndrome, thiamine B1 deficiency is especially dangerous [18].

The body's dopamine and serotonin concentrations, which control mood and pleasure centers, are assumed to be impacted by the active metabolite of Vitamin D. Low nutrient levels may contribute to depression and other mental illnesses because vitamin D is essential for normal brain function. A vitamin D deficiency during infancy may be linked to schizophrenia [19].

The primary omega-3 and omega-6 long-chain polyunsaturated fatty acids (PUFA) in the brain are DHA and AA. Due to their ability to regulate basic neurobiological processes, particularly those related to mood and cognition, both long-chain polyunsaturated fatty acids (PUFA) play crucial roles in brain physiology. Important processes in mood and cognition, neurotransmission, are modulated by DHA and AA. A person's mood and mental clarity are negatively impacted by deficiencies in these vital fatty acids [19].

1.4. Long-term Consequences

Long-term nutritional deficiencies often lead to the development of chronic disease in life and during pregnancy these deficiencies can cause developmental issues.

1.4.1. Chronic diseases

One of the main causes of CDDs (Chronic Degenerative Diseases), according to the Global Burden of Disease, is inadequate nutrition. Malnutrition can cause diseases and chronic health conditions. Chronic degenerative diseases are the leading cause of prolonged disability and death worldwide. These diseases are primarily represented by obesity, cardiovascular disease (CVD), diabetes, chronic kidney disease (CKD), inflammatory bowel diseases, osteoporosis, sarcopenia, and neurodegenerative diseases like Huntington's disease (HD), rheumatoid arthritis (RA), chronic respiratory diseases, and many cancers [20].

In a study involving fifty teenagers in Brazil, it was discovered that boys who experienced early-life undernutrition-related growth stunting acquired five percent more fat mass over three years than their counterparts who did not experience this condition. According to additional research, less than 10% of adolescents without growth retardation in Brazil had high blood pressure, whereas 21% of adolescents with growth retardation had the same condition [21].

1.4.2. Developmental issues

Nutrition is crucial during pregnancy and infancy, as they are critical periods for brain formation and cognitive, motor, and socio-emotional skills development. Inadequate iron intake in the first 2 years of life can negatively impact cognitive functions. Infants with iron deficiency anemia (IDA) are more likely to have poorer cognitive development, even at 5 years old [22].

Undernutrition can take four main forms: underweight, stunting, wasting, and vitamin and mineral deficiencies. Child mortality and morbidity are greatly increased in cases of undernutrition. The term "wasting" refers to low weight for height. A person who has experienced severe weight loss in the recent past may have been malnourished or may have contracted an infectious disease like diarrhea. There is a greater chance of death for a young child who is moderately or severely wasted, but there is treatment available.

Stunting is high height for age. It arises from recurrent or chronic undernutrition, which is typically linked to low socioeconomic status, inadequate nutrition and health of mothers, recurrent illnesses, and/or improper feeding and care of infants and young children in infancy. The physical and cognitive potential of children is hindered by stunting. Underweight kids are those who weigh less than average for their age. Stunting, wastedness, or both can be present in an underweight child.

Enzymes, hormones, and other compounds necessary for healthy growth and development can be produced by the body with the help of micronutrients. From the perspective of global public health, iodine, vitamin A, and iron are the most crucial; a shortage of any of these poses a serious risk to the growth and well-being of people everywhere, especially children and expectant mothers in developing nations.

2. Common Nutritional Deficiencies

2.1. Vitamins deficiency

Vitamin deficiency or avitaminosis or hypovitaminosis occurs due to prolonged lack of a vitamin. It can be primary deficiency (caused by insufficient intake of a vitamin) or secondary deficiency (caused by an underlying disorder such as malabsorption).

2.1.1. Vitamin A deficiency

According to world health organization, vitamin A deficiency is a disabling and potentially fatal public health problem for children under 6 years of age, and related blindness is most prevalent in children under 3 years of age. The increased mortality reached from concurrent infection extends at least 6 years of age and is associated with both clinical and sub clinical vitamin A deficiency. Plasma concentration of retinol falls to below 20 µg/dL, is state of vitamin A inadequacy.

Vitamin A deficiency causes Xerophtalmia, and is a leading cause of preventable blindness, and it also leads to night blindness by drying by out tear ducts of eyes and causes serious damage to cornea (the outer layer of eye) [23]. Vitamin A deficiency can cause night blindness (nyctalopia) and keratomalaysia resulting in permanent

blindness, and if remained untreated, it is a leading cause of preventable child blindness of over 250000 to 500000 children in the developing countries every year [24].

In addition to them, non- specific symptoms include increased morbidity and mortality, poor reproductive health (such as troubled conceiving and infertility), increase risk of anemia and contribution to slow growth and development.

2.1.2. Vitamin B12 deficiency

Vitamin B12 (Cobalamin) deficiency is most commonly seen in vegans. The deficiency leads to megaloblastic and macrocytic anemia (symptoms includes fatigue, weakness etc.), and pernicious anemia (due to cobalamin malabsorption). The deficiency may also cause neuropsychiatric disorders, methylmalonic acidemia, subacute combined degeneration of spinal cord, and potential long-term consequences on nervous system including neurological symptoms (in severe conditions) such as tingling, numbness, cognitive impairment etc [25-27].

2.1.3. Vitamin C deficiency

Vitamin C or Ascorbic acid deficiency is rare. Scurvy occurs after 3 months without consumption of ascorbic acid, as plasma concentrations fall less than 0.2 mg/dL, while the normal plasma concentrations range is 0.4 – 1.5 mg/dL [28]. The deficiency can result in impaired immunity and higher susceptibility to infections. Vitamin C deficiency can lead to weight loss, weakness, and general pains and aches. Longer-term depletion affects the connective tissues, bleeding from the skin, and severe gum disease [29, 30].

2.1.4. Vitamin D deficiency

Vitamin D deficiency is common, and is usually due to low sun exposure. Levels of vitamin D are measured by measuring (25(OH) D) levels in the plasma and deficiency is confirmed if it is below 10 ng/mL [31]. vitamin D deficiency is a worldwide cause of rickets (failure or delay in endochondral ossification at the growth plates of long bones) in children and osteomalacia (defective mineralization of osteoid on the trabecular and cortical surfaces of bone) in adults, both may be associated with pain,

hypocalcemic fits, and muscle weakness in the limbs, heart, and respiratory systems [32].

2.1.5. Vitamin E deficiency

Vitamin E deficiency is rare. Alpha tocopherols deficiency usually occurs by the combination of diets with low amounts of vitamin E, and inadequate consumption of fats, proteins and calories. According to the Institute of Medicine of the US, deficiency occurs if its blood concentration is below 12 μmol/L. Vitamin E deficiency can lead to Ataxia with vitamin E deficiency (AVED), which is a rare autosomal recessive neurodegenerative disease, due to mutations in TTPA gene. Deficiency may also causes a poor conduction of electrical impulses along the nerves due to the changes in the nerve membrane structures and functions [33-34].

2.1.6. Vitamin K deficiency

Deficiency of vitamin K, which is rare, can cause bleeding gums, nosebleeds, heavy menstrual bleeding in women, and sensitivity to bruising. In case of infants, vitamin K in plasma is low at birth, even if a mother is supplemented during pregnancy, as the vitamin is not transported through the placenta. Vitamin K deficiency bleeding (VKDB) is a serious risk for the premature and term baby and young infants. If left untreated, consequences can result in brain damage or even death. The recommended preventive treatment is intramuscular injection of 1 milligram of vitamin K (intramuscular injections are preferred over oral ingestion) [35] at birth known as the Vitamin K shot [36].

2.2. Minerals Deficiency

Mineral deficiencies negatively affect billions of people throughout the world which impose heavy burden on economic productivity and well-being.

2.2.1. Iron

Iron deficiency is most common deficiency among all nutritional deficiencies, and premenopausal women and children are most vulnerable to it. Iron deficiency can

affect the behavior and learning abilities as well as development and growth of a child. Severe anemia can increase the risks of maternal death and pregnancy complications. Iron deficiency anemia is most commonly seen during early childhood and late infancy (when iron stores have been exhausted and milk, which is very poor in iron, is a main food), during the adolescent growth spurt, and in women during childbearing years, due to blood loss during menstruation, and due to the additional iron requirements of pregnancy. Iron depletion leads to microcytic hypochromic anemia which is characterized by small red blood cells which contain less hemoglobin than usual. Severe iron deficiency anemia can lead to pale skin, difficulty breathing on exertion, fatigue, weakness, apathy, and low resistance to cold temperatures [37].

2.2.2. Calcium

Calcium has a direct link with the health of bones and teeth. Calcium deficiency, during childhood, may predispose individual to osteoporosis (reduced bone mass as bones lose density, and develop fragility and results in fractures, mostly of the hip) later in life. Osteoporosis is mainly common is postmenopausal women [37, 38].

2.2.3. Magnesium

Magnesium (an essential cation) is involved in many enzymatic reactions, and is critical in energy-requiring metabolic processes, as well as protein synthesis and anaerobic phosphorylation. Poor nutrition, gastrointestinal and renal diseases, type 2 diabetes, alcoholism, stress, and certain medications may lead to magnesium deficiency. Magnesium deficiency can lead to personality changes, including apathy, depression, agitation, confusion, anxiety, and delirium. Hypomagnesemia may also lead to a wide variety of clinical presentations, including neuromuscular irritability, cardiac arrhythmias, and increased sensitivity to digoxin [39, 40].

2.2.4. Zinc

Zinc is a constituent of numerous enzymes, and plays structural roles in proteins. Its deficiency was first reported in 1960s. Zinc Deficiency can be due to diet low in meat (low protein foods) and high in unleavened breads, and whole-grain diets which

contain phytic acid, and other anti-nutritive factors that inhibit the absorption of zinc. Clay eating also affects the absorption of zinc and contributes to zinc deficiency. Inherited zinc-responsive syndrome called acrodermatitis enteropathica also involves severe zinc deficiency. Zinc deficiency may include symptoms like diarrhea, increased susceptibility to infections, skin lesions, poor appetite, hair loss, reduced taste and smell acuity, slow wound healing, impotence, and low sperm count. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases the susceptibility to infection [37, 41].

2.2.5. Iodine

Globally, 2 billion individuals have an insufficient iodine intake, and South Asia and sub-Saharan Africa are particularly affected, and about 50% of Europe remains mildly iodine deficient [42]. Iodine deficiency is generally recognized as the most common cause of preventable mental retardation and the most common cause of endocrinopathy including goiter (formation of a visible lump at the front of the neck due to enlargement of thyroid gland in chronic iodine deficiency) and primary hypothyroidism. Lower cognitive and neuromuscular deficits are other consequences of chronic deficiency. Iodine deficiency becomes particularly critical in pregnancy due to the consequences for neurological damage (cretinism) during fetal development (may also cause miscarriage or stillbirth), as well as during lactation [37, 43].

3. Symptoms and Health Effects of Nutritional Deficiencies

Nutritional deficiencies are manifested as various physical and psychological symptoms. These deficiencies can impair cognition and affect mental function. Furthermore, these symptoms are age specific. If left untreated, they can have long-term implications and can lead to a decreased quality of life.

3.1. Physical Manifestations

3.1.1. Fat Soluble Vitamins

Vitamin A deficiency has been commonly associated with numerous ocular symptoms. It leads to xerophthalmia which is characterized by corneal xerosis, conjunctival xerosis,

Bitot's spots, nyctalopia (night blindness), xerophthalmic fundus (lesions on retina), and corneal ulcers. Unaddressed xerophthalmia leads to keratomalacia (softening of cornea) which can progress to permanent loss of vision [44]. Other manifestations of vitamin A deficiency include various skin problems such as dry and scaly skin, dry lips, fine wrinkles, thickened tongue, and follicular hyperkeratosis (excess keratin), poor wound healing, delayed growth and development, and weakened immune system since vitamin A is required for the maintenance of integrity of epithelial barrier, stimulation of epithelial growth and collagen synthesis, normal keratinization, and maturation of various immune cells [45, 46].

Vitamin D deficiency causes bone pain and is the most common cause of osteomalacia and rickets. It can also worsen osteoporosis by decreasing bone mass. Chronic muscle pain, muscle weakness, and fatigue have been associated with vitamin D deficiency [47]. Deficiency of vitamin D in infancy has been associated with development of type-1 diabetes later in life [48]. Low vitamin D levels have been linked to various skin problems like atopic dermatitis and bullous pemphigoid, and alopecia areata [45]. Its deficiency may also play a part in acne development [49]. Vitamin D deficiency plays a role in exacerbating asthma [50]. It has also been linked to mood changes such as anxiety and suicidal ideation [51, 52]. Vitamin D deficiency has also been associated with a greater risk of viral infections, such as COVID-19 [53].

Cutaneous manifestations of vitamin E deficiency include follicular hyperkeratosis and petechiae [54]. Other symptoms include ataxia, decreased vibratory sense, hyporeflexia, muscle weakness, decreased night vision, and limited upward gaze. Severe deficiency of vitamin E may lead to dementia, blindness, and cardiac arrhythmias [55].

Vitamin K deficiency manifests itself through various symptoms including petechiae, purpura, gum bleeding, epistaxis, melena, and hematuria [54, 56]. In women, vitamin K deficiency leads to menorrhagia [57].

3.1.2. Water Soluble Vitamins

Vitamin B1 (Thiamine) deficiency affects the nervous, immune, and cardiovascular systems. It is the cause of wet beriberi which causes symmetrical peripheral neuropathy, dry beriberi which causes heart failure, and Wernicke-Korsakoff syndrome which alters the CNS function leading to problems with gait, mental status, and ocular function. Thiamine deficiency leads to anorexia, double vision, vertigo, loss of feeling in extremities, memory loss, and confusion [58].

Cutaneous manifestations of vitamin B2 (Riboflavin) deficiency include stomatitis, glossitis, cheilitis, pharyngitis, seborrheic dermatitis, and hair loss [54]. Riboflavin deficiency can also cause blurred vision, fatigue, and depression [59].

Vitamin B3 (Niacin) causes pellagra which is characterized by diarrhea, dementia, and dermatitis and can lead to death. Hyperpigmented rash on body's sun-exposed areas along with glossitis is seen in dermatitis associated with pellagra. Other symptoms of niacin deficiency include a beefy red tongue, malar rash, loss of appetite, muscle weakness, depression, irritability, lethargy, confusion, and paresthesias [60].

Vitamin B5 (Pantothenic acid) deficiency leads to myelin loss, neurodegeneration, acetylcholine deficiency, and Huntington disease [61].

Vitamin B6 deficiency is the cause of severeal skin lesions including glossitis, periorificial dermatitis, and pellagra-like skin lesions because it causes niacin deficiency.

Vitamin B7 (Biotin) deficiency leads to diffuse alopecia, dermatitis of the central face, and brittle nails. Affected individuals may also experience conjunctivitis, myalgia and paresthesias [54, 62].

The physical exam of a patient with vitamin B9 (Folic acid) deficiency may reveal a beefy red tongue that's painful, pale skin, and certain exfoliative skin disorders [63]. Maternal folic acid deficiency is associated with several congential anomalies such as cleft lip, congenital heart disease, and spina bifida. Folic acid deficiency may also lead to eye problems as it is required for optimal eye health [64].

Vitamin B12 (Cobalamin) deficiency leads to cheilits, glossitis, stomatitis, and sebhorreic dermatitis, megaloblastic anemia and weight loss [54].

Vitamin C deficiency is commonly associated with scurvy which manifests as gingival inflammation, bleeding gums, tooth loss, and fatigue. Vitamin C deficiency also leads to follicular hyperkeratosis with corkscrew hair and poor wound healing [54].

3.1.3. Minerals

Iron deficiency leads to pale skin, pale conjunctiva, koilonychia (spoon-shaped nails), cold hands and feet, and fatigue [54].

Calcium deficiency leads toincreased dental caries alopecia, exfoliative dermatitis, enamel hypoplasia, shortened premolar roots, thickened lamina dura, psoriasis, impetigo herpetiformis, subcapsular cataracts, and papilledema [65]. It is the major cause of tetany and osteoporosis. Chvostek's sign is seen in hypocalcemic patients with increased neuromuscular excitability. It happens when tapping of the facial nerve in front of the ear leads to an ipsilateral contraction of the facial muscles [66].

Magnesium deficiency negatively affects bone and muscle health [67]. It may lead to muscle cramps, weakness, fatigue, and seizures [68].

Zinc deficiency causes acrodermatitis enteropathica, which is characterized with pustular or vesicular rashes in the perioral, perineal, and acral areas of the body. It may also lead to diffuse alopecia, dysgeusia, anorexia, diarrhea, growth retardation, and infertility [54].

Iodine deficiency leads to goiter (enlarged neck), myxedematous cretinism, and neurological cretinism. The myxedematous form is characterized by severe hypothyroidism with dwarfism (short stature), dry skin, mental retardation, and delayed sexual maturation. While, the neurological form is characterized by severe mental deficiency, inability to stand or walk, motor spasticity, and deaf mutism [69].

3.2. Cognitive and Mental Effects

Nutritional deficiencies that can lead to a decline in cognitive and mental function include vitamin A, vitamin D, vitamin B1, vitamin B6, vitamin B9, vitamin B12, vitamin E, iron, calcium, magnesium, and zinc.

Vitamin A helps to maintain neuronal plasticity and cognitive function in adults. Vitamin A deficiency leads to cognitive decline and is also associated with Alzheimer's disease [70].

Vitamin D is important for brain development and function [71]. Low vitamin D leads to poor cognition and is associated with mood changes, dementia, and Alzheimer's disease [72, 73]. Vitamin A and D co-deficiency exacerbates symptoms of children with autism spectrum disorder [74].

Thiamine (B1) is present in the brain and the peripheral nervous system where it plays an important role in nerve impulse conduction [75]. Its deficiency leads to confusion, memory impairment, loss of coordination, and paralysis. Severe deficiency, although rare, leads to beri-beri and Wernicke-Korsakoff syndrome [71].

Vitamin B6 is involved in regulating mood and mental function. Its deficiency leads to migraines, depression, and convulsions [71]. Low vitamin B6 levels are associated with hyperhomocysteinemia which increases the risk of cognitive decline and Alzheimer's disease [76].

Folic acid (B9) deficiency leads to neural tube defects in fetus and neurological abnormalities in adults. Its deficiency leads to hyperhomocysteinemia, increased levels of homocysteine in blood, which causes neuro-inflammation and may lead to severe depression [77]. Furthermore, OCD patients also have low serum folic acid levels [78].

B12 is required for the maintenance of the myelin sheath. Its deficiency leads to depression, psychosis, obsessive symptoms, and can compromise antidepressant response. Low vitamin B12 levels are associated with hyperhomocysteinemia which increases the risk of cognitive decline and Alzheimer's disease [71].

Alpha-tocopherol, an isoform of vitamin E, plays an important role in the protection of central nervous system from oxidative stress [79]. Low plasma vitamin E levels are positively associated with the risk of Alzheimer's disease [80]. Prolonged and severe deficiency may lead to dementia [81].

Iron deficiency leads to cognitive deficit. It impairs intelligence, attention span, and sensory perception functions, and affects behavior and emotions [82].

Calcium is required for neurotransmission regulation and nerve excitability [75]. Deficiency leads to irritability, confusion, disorientation, anxiety, psychosis, poor memory, reduced concentration, personality disturbances, and parkinsonism [65].

Magnesium has anti-inflammatory properties and plays an important role in nerve conduction, synaptic transmission, and membrane stability. Magnesium deficiency leads to migraines, anxiety and depression [77, 83]. Zinc acts as a cofactor and neuro-secretory product in the CNS and is present in many synaptic vesicles of the forebrain. Its deficiency impairs cognition and leads to neuropsychological impairment [75].

3.3. Long-term Implications

Micronutrient deficiency during early stages of life can lead to debilitating life-long consequences. It affects physical growth and development and increases morbidity and mortality [84]. Following are some long-term implications of micronutrient deficiencies:

Neural Tube Defects: It is caused by periconceptional folic acid deficiency. Most common NTDs include spina bifida and anencephaly [84].

Cretinism: It is caused by iodine deficiency leading to low thyroid hormone levels during childhood [69].

Blindness: Vitamin A deficiency in childhood leads to night blindness which may progress to permanent blindness if left unresolved [85].

Low Academic Performance: Anemia in early life, even if resolved later, leads to low academic performance later in life. Vitamin B-12 deficiency could also lead to similar problems [86].

Skeletal Malformations: Deficiency of vitamin A during the 3rd quarter of pregnancy may lead to fetal skeletal malformations [84].

3.4. Specific Effects on Different Age Groups

Certain micronutrient deficiencies lead to specific symptoms in specific age groups. These symptoms along with age groups are discussed below.

Infants and Children

Deficiencies in this age group disrupt normal growth and development and may lead to life-long disabilities affecting quality of life. This age group is particularly more susceptible to micronutrient deficiencies because of their increased requirements [87]. Pre-mature infants have insufficient nutrient stores making them more susceptible to deficiencies of trace elements, especially zinc, selenium, and iron [88]. Following are the outcomes of some of the most common nutrient deficiencies.

Milk Anemia: It results from iron deficiency during late infancy and early childhood due to delayed weaning and high milk intake. The infant is inanimate, has pale skin, anorexia, dysphoria, and poor weight gain [88].

Short Stature (Stunting): Zinc, iodine, and vitamin D deficiencies may lead to short stature in children [86, 88, 89]. Generally, an inadequate food supply during the period of growth leads to short stature [90].

Wasting: It is caused by protein-energy malnutrition resulting from poor nutritional intake [91].

Rickets: It is caused by calcium and vitamin D deficiency in childhood and leads to weak bones that bend easily. Children with rickets have bowed legs, soft skull bones, and thickening of ankles, knees and wrists [92].

Impaired Cognitive Development: Iron, iodine, zinc, and vitamin B12 deficiencies in childhood lead to cognitive deficits [86].

3.5. Females of Reproductive Age

Women of reproductive age, pregnant, and lactating mothers are also considered a high risk group for micronutrient deficiencies because of increased requirements. Deficiencies may lead to fetal anomalies, infertility and other problems. These conditions are discussed below along with the deficiency responsible for it.

Anemia: Iron, vitamin B9, and vitamin B12 deficiencies are most commonly associated with anemia. Menstruation leads to loss of iron which makes females of reproductive age prone to anemia. Other nutrients that play a role in etiology of anemia are vitamin C, vitamin B6, and vitamin D [93].

Infertility: Vitamin D, folate, and iodine deficiency are some of the nutritional causes of female infertility [94, 95].

Fetal Anomalies: Folic acid deficiency before conception leads to neural tube defects in the fetus [84]. Maternal iodine deficiency leads to fetal hypothyroidism. Maternal iron deficiency reduces oxygen-carrying capacity of the fetus and affects fetal immunity, growth, and development [86].

3.6. Elderly

This age group is also at high risk of developing deficiencies due to poor absorption, chronic illnesses, and poor dietary habits.

Osteoporosis: Vitamin D, calcium, magnesium, copper, zinc, and vitamin K deficiencies are associated with osteoporosis, most commonly in females [96].

Neurological Disorders: Deficiencies of certain nutrients, such as vitamin B6, B9, B12, D and E, are linked to Alzheimer's disease and dementia [97]. Hypocalcemia is associated with parkinsonism [65].

Ocular Symptoms: Low levels of vitamin D may lead to posterior subscapular cataracts [98]. It has also been associated with myopia degeneration and glaucoma. Vitamin A, D, and riboflavin deficiencies are associated with age-related macular degeneration [99].

4. Risks and Misconceptions Surrounding Supplements

4.1. Overdosing and toxicity

Nutritional supplements are prescribed to overcome nutritional inadequacies and deficiencies. They complement the diet and their excessive consumption leads to adverse health effects and toxicity. Rarely, overconsumption of water-soluble vitamins such as Vitamin B-complex and Ascorbic acid leads to toxicity. Supplemental toxicity is mostly associated with fat-soluble vitamins such as vitamins A, E, and K, minerals, linoleic, and linolenic acids. Fat-soluble vitamins such as vitamins A, D, E, and K are stored in the liver and adipocytes of our body. Continuous supplemental dosage along with a high intake of these vitamins through diet causes their accumulation. This leads to the symptoms of overdosing and toxicity.

4.1.1. Vitamin A

Hypervitaminosis A is a rare condition that typically results from taking too many supplements or medications. The consumption of large amounts of vitamin A through food and supplementation is the main cause of toxicity. Vitamin A analogs are present in some dermatological drugs, such as isotretinoin. When these drugs are used excessively or for an extended period, vitamin A stores can build up and cause toxicity, teratogenic effects, and hypervitaminosis A.

The recommended daily allowance (RDA) for vitamin A is expressed in retinol activity equivalents (RAE). Interestingly, one RAE is equal to three International Units (IU) or one milligram of retinol. The recommended daily allowance (RDA) for vitamin A is

- 700 RAE for female adults
- 900 RAE for male adults

- 750 to 770 RAE for expectant mothers
- 1200 to 1300 RAE for nursing mothers

The purpose of the tolerable upper intake levels (UL) for vitamin A is to avoid toxicity. The recommended daily allowance (UL) of vitamin A for adults is 3000 RAE. In developed nations, preformed vitamin A from dietary supplements is often consumed more than the recommended daily allowance [100].

4.1.2. Acute Toxicity

Systemic vitamin A toxicity usually occurs when a person takes in more than 100,000 RAE in a brief amount of time, usually from high-dose medications or supplements. Symptoms of toxicity include headache, nausea, vomiting, dizziness, irritability, blurred vision, and dyscoordination of the muscles. Acute toxicity is uncommon and more likely to happen when ingesting synthetic forms of vitamin A, like isotretinoin, a retinoid medication. Cheilitis, as well as dry lips and mucous membranes in the mouth, eyes, and nose, are examples of mucocutaneous effects. The proposed mechanism entails altered barrier function, decreased sebum production, and decreased epidermal thickness. Other cutaneous symptoms include fissuring of the fingertips, peeling of the palms and soles, dry skin, and pruritus. Increased vitamin A dosages may cause telogen effluvium. Increased intracranial pressure and bone pain are possible symptoms of severe cases [100].

4.1.3. Chronic Toxicity

Long-term overconsumption of vitamin A, usually more than 8000 RAE daily, is linked to chronic vitamin A toxicity. This can happen if you take high-dose vitamin A supplements for an extended period or if you consume large amounts of animal-based foods high in preformed vitamin A, like liver. Hepatomegaly, brittle nails, hair loss, exhaustion, loss of appetite, and pain in the bones and joints are some of the symptoms of toxicity. Numerous organ systems are impacted by chronic retinoid poisoning. Hip fractures, osteoporosis, and hypercalcemia can result from bone-related conditions such as bone

spurs, calcinosis, and bone resorption. Headache, nausea, and vomiting are effects of the central nervous system [100].

In the 1950s, research on animals revealed the teratogenic effects of vitamin A consumption. Many studies have since been carried out to determine the fundamental reasons behind the effects. Several congenital abnormalities in humans have been linked to excessive vitamin A intake during pregnancy. Abnormalities in the central nervous system, such as microcephaly and hydrocephalus; cardiac problems, such as transposition of the great vessels; craniofacial deformities, such as cleft lip and palate; limb abnormalities; and urinary tract disorders are among the disabilities linked to this condition [100].

4.1.4. Vitamin D

Vitamin D toxicity in healthy individuals can arise from intentional or inadvertent overconsumption of vitamin D supplements. Toxicological effects can also arise from prescription errors that are not followed up on with regular monitoring of vitamin D levels. Toxicity resulting from lack of monitoring is frequently seen in patients requiring high doses to treat ailments like osteoporosis, renal osteo-dystrophy, psoriasis, gastric bypass surgery, celiac, or inflammatory bowel disease.

In the National Poison Data System, vitamin D exposure was linked to 11,718 cases, according to the most recent report from America's Poison Centers (APC). The majority of these cases involved children under the age of five. Intentional exposures accounted for the great majority of cases. The total number of cases of vitamin D toxicity exceeded the total number of cases of vitamin toxicity (B, A, C, and E combined). This demonstrates how the use of vitamin D supplements is prevalent.

The Endocrine Society clinical practice guidelines suggest that the RDA of vitamin D is.

- From birth to 12 months is 400 IU/d.
- For children 1-13 and teenagers 14-19 600 IU/day
- For adults aged 19 to 70 years is 600 IU/d.

- For adults above 70, RDA is at least 800 IU/d

The maximum suggested daily requirement is 4000 IU/d for everyone older than 8 years [101]. Hypercalcemia primarily causes the symptoms of vitamin D toxicity. Nausea vomiting, decrease in appetite dehydration, constipation, frequent urination, polydipsia, muscle weakness, confusion, lethargy and fatigue, bone pain, and kidney stones are all symptoms of Vitamin D toxicity.

4.1.5. Vitamin E

For months or years without any apparent side effects, a lot of adults consume relatively large doses of vitamin E (alpha-tocopherol 400 to 800 mg/day). Fatigue, diarrhea, nausea, and muscle weakness can occasionally happen. Bleeding represents the greatest risk. But bleeding rarely occurs unless the patient is taking oral coumarin or warfarin, or the dose is greater than 1000 mg/day. For adults over 19, the maximum amount of tocopherol that they can consume is 1000 mg. High supplementation with vitamin E may raise the risk of hemorrhagic stroke and early mortality, according to analyses of earlier research. Stopping the vitamin or lowering consumption to less than the daily maximum of 1000 mg is the recommended course of action for treating vitamin E poisoning [102].

4.1.6. Vitamin K

Dietary vitamin K is called phytoquinone, or vitamin K1. Vegetable oils, soybeans, and leafy greens (particularly collards, spinach, and salad greens) are among the sources. Dietary fat improves its absorption. Infant formulas have extra vitamin K in them. Following the neonatal stage, the gastrointestinal tract's bacteria produce vitamin K, which the body absorbs and uses. Menaquinones, a class of compounds produced by intestinal tract bacteria, are referred to as vitamin K2. However, the quantity of these compounds synthesized is insufficient to meet the body's need for vitamin K. Although rare, vitamin K toxicity is most common in infants who are formula-fed. Vitamin K toxicity can result in jaundice and hemolytic anemia. Kernicterus can result from jaundice in infants.

4.2. Essential Fatty Acids Supplementation

4.2.1. Omega 3 Fatty Acids

DHA, eicosapentaenoic acid (EPA), and a-linolenic acid (ALA) are the three omega-3 polyunsaturated fatty acids (PUFAs) that are most clinically relevant. Right now, icosapent ethyl and omega-3-acid ethyl esters, two prescription omega-3 fatty acid products, are approved by the FDA for use. Adults (above the age of eighteen) with extremely high triglycerides (greater than 500 mg/dl) may use isosapent ethyl and omega-3-acid ethyl esters as a dietary supplement to lower triglyceride levels and lower angina. The general consensus is that EPA and DHA are safe. According to FDA guidelines, the daily intake of EPA and DHA combined should not exceed 3 g/day, with supplements providing no more than 2 g/day. When taking high doses, prudence is required as it may cause bleeding issues and lower immune function due to changes in the inflammatory reaction [103].

Digestion-related adverse effects, such as nausea, bloating, burping, upset stomach, and loose stools, are possible with omega-3 supplements. Reduced blood clotting in healthy adults is one of the potential side effects of omega-3 supplements, according to a 2013 study. Immune System Dysfunction: According to a 2013 scientific review, "excess omega-3 fatty acids can alter immune function sometimes in ways that may lead to a dysfunctional immune response to a viral or bacterial infection."

4.2.2. Omega 6 Fatty Acids

According to some research, eating too many omega-6 fats may cause a number of health issues. A 2018 study discovered a link between inflammation that results in disease and tissue damage and an increased dietary intake of omega-6 fats. According to the Arthritis Foundation, omega-6 fatty acids may cause the body to produce more pro-inflammatory chemicals, which could exacerbate arthritis sufferers' symptoms. Diets high in omega-6 fats have been associated with obesity in other research. Further clinical trials are necessary, according to other researchers, and there is no clear consensus regarding the role of omega-6 fatty acids in causing or preventing inflammation. Furthermore, some encouraging research results have been reported. For

instance, a review of thirty studies revealed a correlation between a lower risk of heart disease and increased body levels of omega-6 fats.

4.3. Water-Soluble Vitamins

Unlike fat-soluble vitamins water-soluble vitamins do not have any storage site. The excess of these vitamins is usually excreted out of the body via urination. These vitamins include vitamin C, and eight B vitamins: Vitamin B1 (thiamine), Vitamin B2 (riboflavin), Vitamin B3 (niacin), Vitamin B5 (pantothenic acid), Vitamin B6 (pyridoxine), Vitamin B7 (biotin), Vitamin B9 (folate), Vitamin B12 (cobalamin). However, when taken in excess some of these vitamins can have adverse effects.

Like Vitamin K, certain water-soluble vitamins, have no detectable toxicity and thus no established UL. These vitamins include thiamine (vitamin B1), riboflavin (vitamin B2), pantothenic acid (vitamin B5), biotin (vitamin B7), and cobalamin (vitamin B12).

Vitamin C: Although vitamin C has low toxicity, large dosages might produce gastrointestinal problems such as cramps, diarrhea, vomiting and nausea. Migraines can occur at a daily intake of 6 grams.

Vitamin B3 (niacin): Nicotinic acid ingested in high amounts of 1-3 grams per day, niacin can cause impaired vision, abdominal pain, high blood pressure, and liver damage.

Vitamin B6 (pyridoxine): Long-term B6 overconsumption can result in severe neurological symptoms, skin lesions, light sensitivity, nausea, and heartburn, with some of these symptoms occurring at 1-6 grams per day.

Vitamin B12 (Cobalamin): Taking too much folate or folic acid as a supplement may impair mental function, harm the immune system and conceal a potentially serious vitamin B12 deficiency.

4.4. Minerals

Minerals are regulated in our body via the excretory system. There is a potential for supplements of minerals to cause imbalance and symptoms of the overdose appear.

4.4.1. Calcium

Among healthy individuals taking supplements containing 1,500–4,000 mg of calcium daily, constipation, bloating, nausea, and intestinal gas are frequently reported side effects. Kidney damage may result from doses exceeding 4,000 milligrams per day [104].

9.4.2. Magnesium

Overdose of magnesium rarely causes toxicity but in individuals having chronic health conditions the overload can cause irregular heartbeat, muscle weakness, breathing difficulty, and cardiac arrest [104].

4.4.2. Iron

Consuming excessive amounts of iron supplements, particularly in young children, can be fatal. Even 3 grams (3,000 milligrams) of elemental iron at one time can be the fatal dose for a small child. This is how much elemental iron is contained in 60 tablets, each containing 50 milligrams. In adults, 200–250 mg of elemental iron per kilogram (2–2 pounds) of body weight is thought to be the lethal dose. Zinc absorption and plasma zinc concentrations, however, can be decreased by supplements that contain 25 mg of iron or more. Abdominal pain, nausea, vomiting, diarrhea, and upset stomach are among the gastrointestinal side effects that high-dose iron supplements may cause. When taken in combination with food, supplements, or medications, acute intakes of more than 20 mg/kg iron (approximately 1,365 mg iron for a 150-pound person) can cause corrosive necrosis of the intestine, which can result in shock, tissue damage, and organ failure, and loss of fluid and blood. Overdosing on iron can result in multisystem organ failure, coma, convulsions, and even death. A single 100 mg/kg ingestion of iron is equivalent to 4,090 mg for a 150 lb person [104].

4.4.3. Zinc

Abdominal distress, headaches, nausea, vomiting, and anorexia can all be symptoms of high zinc intake. Doses of 50 mg or more of zinc, usually from supplements or overuse of zinc-containing denture adhesive creams, can disrupt the body's ability to absorb

copper (which can lead to low copper status), weaken the immune system, and lower HDL cholesterol if taken for weeks. Moreover, very high supplement doses of zinc (142 mg/day) may disturb the equilibrium of magnesium and impede its absorption. Immune system interference may occur from doses 27 to 37 times the RDA (11 mg for men and 8 mg for women) [104].

4.4.4. Iodine

Goiter, increased TSH levels, and hypothyroidism are among the symptoms of iodine deficiency that can be brought on by high iodine intakes. This is because excess iodine in susceptible people inhibits thyroid hormone synthesis, which raises TSH stimulation and can result in goiter. Thyroiditis and thyroid papillary cancer are also linked to high iodine intake, according to studies. Rarely, large doses of iodine can result in acute iodine poisoning, typically involving grams. The symptoms of acute poisoning include fever, chills, nausea, vomiting, diarrhea, weak pulse, and coma in addition to burning in the mouth, throat, and stomach [104].

4.4.5. Fluoride

Fluorosis, or brown patches on teeth, brittle bones, exhaustion, and muscle weakness are caused by large doses of fluoride. High fluoride dosages over an extended period may also result in tiny bone bumps on the spine.

4.4.6. Selenium

Consuming poorly designed over-the-counter products that contain excessive amounts of selenium has led to acute selenium toxicity. Acute selenium toxicity can result in severe neurological and gastrointestinal symptoms, acute respiratory distress syndrome, myocardial infarction, hair loss, muscle soreness, tremors, lightheadedness, facial flushing, kidney failure, cardiac failure, and, in rare circumstances, death.

4.5. Interaction with medications

Nutritional supplements and prescription medications can interact in ways that can affect how your body absorbs and uses both. Combining vitamins with prescription

drugs can change how effective they are, raise the possibility of side effects, or even cause unanticipated health problems.

Experts warn that taking certain medications and supplements concurrently may have harmful, even fatal effects. Even though using dietary supplements and pharmaceuticals is common, especially among older adults. According to the National Center for Complementary and Integrative Health (NCCIH), many people take prescription or over-the-counter (OTC) medications along with supplements without realizing the possibility of interaction. Generally, dietary supplements interact with medicines in four ways.

1. Reduced Medication Effectiveness: Some supplements can interfere with the absorption or metabolism of medications, reducing their effectiveness.

2. Increased Side Effects: Mixing certain medications with supplements might intensify side effects.

3. Toxicity: Certain supplements, especially when taken in high doses or combined with specific medications, can lead to toxicity.

4. Altered Medication Levels: Supplements can affect the levels of medications in your bloodstream.

Following are some prominent supplement-medicine interactions.

4.5.1. Iodine supplements

Iodine supplements can interact with various medications, including antithyroid medications like methimazole, and angiotensin-converting enzyme inhibitors like benazepril, lisinopril, and fosinopril, which can cause hypothyroidism. Additionally, taking potassium iodide with ACE inhibitors can increase the risk of hyperkalemia, and potassium iodide with potassium-sparing diuretics can also increase hyperkalemia [104].

4.5.2. Vitamin E

Vitamin E may affect the use of chemotherapy drugs, anticoagulants, anti-platelet drugs, herbs, and supplements, increasing the risk of bleeding. It should be used cautiously with CYP3A4 substrates, statins, and niacin, which may reduce their effect on high-cholesterol individuals. Additionally, combining vitamin E with vitamin K may decrease its effects [102].

4.5.3. Vitamin D

Orlistat, a weight-loss drug, can decrease vitamin D absorption. High-dose vitamin D supplements may affect cholesterol-lowering statins, while steroids like prednisone can lower vitamin D levels. Thiazide diuretics may raise calcium levels too high [104].

4.5.4. Calcium

Dolutegravir, an HIV integrase inhibitor, can be reduced by calcium supplements, while levothyroxine, a thyroid hormone, can be interfered with by calcium carbonate supplements. Long-term lithium use can lead to hypercalcemia, and concurrent use of calcium supplements and quinolone antibiotics can reduce their absorption. FDA-approved labels advise patients to take dolutegravir 2 hours before or 6 hours after calcium supplements [104].

4.5.5. Iron Supplements

Iron can interact with certain medications, such as levodopa, levothyroxine, and proton pump inhibitors. Iron supplements can reduce the absorption of levodopa, a medication used to treat Parkinson's disease and restless leg syndrome, and may diminish its clinical effectiveness. Iron supplements can also reduce the absorption of levothyroxine tablets, which can be clinically significant in some patients. Proton pump inhibitors, which reduce stomach acidity, can also reduce iron absorption. Patients with iron deficiency taking these inhibitors may have suboptimal responses to iron supplementation [104].

4.5.6. Vitamin K

Warfarin (Coumadin) can interact with vitamin K, so it's crucial to maintain a consistent daily intake of vitamin K from food and supplements. Antibiotics can destroy gut bacteria that produce vitamin K, potentially reducing the body's absorption of this nutrient. Bile acid sequestrants, like cholestyramine and colestipol, can also reduce vitamin K absorption, especially if taken for extended periods. Weight-loss drug Orlistat can also decrease vitamin K absorption. It's essential to inform healthcare providers about dietary supplements and prescription or over-the-counter medicines to avoid potential interactions or interference with the body's absorption, use, or breakdown of nutrients like vitamin K [104].

4.5.7. Folate

In cancer treatment, folate supplements may interfere with methotrexate (Rheumatrex, Trexall). Antiepileptic or anti-seizure drugs such phenytoin (Dilantin), carbamazepine (Carbatrol, Tegretol, Equetro, Epitol), and valproate (Depacon) may lower folate levels in the blood. Taking folate supplements may also lower blood levels of these drugs. Sulfasalazine (Azulfidine) treatment for ulcerative colitis may impair the body's ability to absorb folate, resulting in folate insufficiency [104].

5. Role of Supplements

The National Institutes of Health (NIH) defines nutritional supplements as goods meant to improve or complement the food you eat. Minerals, vitamins, botanicals, amino acids, herbs, enzymes, and other components can be found in these types of goods.

The FDA explains definition of supplement in different way which is explained below:

The purpose of nutritional supplements is to enhance or complement a meal plan. Its goals include illness prevention, diagnosis, treatment, and recovery. Supplements can be taken and are available in a variety of forms, such as liquids, tablets, capsules, candies, bars, soft gels, and gel caps [105].

A nutritional supplement is defined as a "good consumed through the mouth containing a "dietary ingredient" meant to enhance the food" by the Food and Drug Administration, the US government's regulating body. "The nutritionist ingredient(s)" has been further defined as "one or an assortment of vitamin, mineral, herb, amino acid, enzyme, concentrates or extracts" under the Nutritional Supplement Health and Education Act of 1994 [106].

5.1. Types of Supplements available in market

There are many supplements available in market in form of multivitamins, minerals or vitamins some of them are listed below:

5.1.1. Nouri Stay Well

A drink mix that supports the immune system and contains probiotics, also immunobiotics, and prebiotics. Enriched with Zinc, Magnesium, B12, B3, D3, and C vitamins. A way to help your immune system and intestinal health every day as it contains no sugar, no calories, no artificial sweeteners or colors.

5.1.2. Ritual Gut Health Synbiotic

Prebiotic, probiotic, and post biotic combined every day with two of the most scientifically researched probiotic strains worldwide. Free of gluten and other common allergies, non-GMO, and vegan. Probiotics may assist immune function and provide occasional relief from gas, bloating, and diarrhea. Intended to support the growth of beneficial bacteria in the gut.

5.1.3. Ritual Essential For Men Multivitamin

- Ten elements that can be traced
- Mint-infused for a zesty taste
- Capsule for release later on
- Free of gluten and significant allergens
- Essential nutrients improve heart, brain, and immune system health

5.1.4. Ritual Essentials Multivitamin For Women

- Capsules with delayed release
- Composed of nine detectable components
- Mint-infused for a crisp flavor
- Designed to close nutritional shortages
- Free of main allergens and gluten

5.1.5. Centrum Women

- Contains nutrients that aid in the maintenance of healthy bones, such as calcium.
- Additional Omega-3 DHA derived from microalgae to support heart health maintenance
- Lichen provides vitamin D3, which supports healthy immunological function

5.1.6. Garden of Life Vitamin Code

- Composed of minerals that aid in the maintenance of healthy bones and calcium
- An additional source of Omega-3 DHA from microalgae to support heart health
- Lichen-derived vitamin D3 supports healthy immune system function

5.1.7. Transparent Labs Whey Protein Isolate

- Each 34-gram scoop contains 28 grams of protein
- Sourced from American dairy animals that are finished and fed entirely on grass
- Enhances muscle growth and recuperation while advancing general well-being and longevity
- Made from hormone-free, naturally-fed whey

5.1.8. Ritual Essential Protein

- 150 mg of choline and 20g of protein
- Support the development of lean muscle and aid in muscle recovery following exercise each serving offers the full spectrum of amino acids
- Protein derived from plants without alcohol from sugar

5.1.9. Kaged Plantein Protein Powder

- Delivers Whole BCAAS & EAAS
- Used essential components like natural millet and coconut MCT oil to produce a smooth, velvety mouthfeel
- Free of gluten, lactose, soy, or dairy
- Organically flavored and sugar-free (0g)
- Muscle Milk Genuine Protein Powder, Vanilla Crème
- Contains 28 grams of protein per scoop
- Made from naturally fed, hormone-free whey
- No artificial sweeteners, colors or flavors

5.1.10. New Chapter Organics Men's Advanced Multivitamin

- Ten elements that can be traced
- Important components promote heart, brain, and immune system health
- Mint-infused for a zesty taste

5.1.11. Garden of Life Vitamin Code Raw Men

- Includes gastrointestinal enzymes along with living microbes
- Free of gluten, soy-free, vegan
- Includes a combination of natural, uncooked vegetables and fruits

5.1.12. Centrum Men

- GMO-free and gluten-free
- Contains zinc as well as beta-carotene to strengthen the body's defenses

5.1.13. Elements Vitamin C

- Rich in Zinc, Magnesium, B12, B3, D3, and C vitamins
- None at all. There are no calories and no sugar substitutes or colors
- Even with a single packet each day, your system will be optimally equipped to handle obstacles

5.1.14. Solgar Vitamin C

- These capsules are vegan, kosher, gluten-free, and dairy-free

- They are made from rose hips, which are the seed pods of rose plants that have been shown to have antioxidant properties, according to Amidor
- Additionally, they don't include any yeast, wheat, soy, sugar, salt, or artificial flavors or sweeteners

5.1.15. HUM Base Control Multivitamin

- Contains 22 vital micronutrients to bridge dietary deficiencies in nourishment and iron that promote the synthesis of red blood cells
- Fulfills major nutritional recommendations for daily consumption
- Enhances general wellness and good health

5.1.16. Pure Encapsulations Iron-C

- It offers 15 milligrams of iron, which is almost the Daily Value but not excessive
- 175 milligrams of vitamin C
- Improves the human body's ability to absorb iron
- Two types of iron are aspartate and glycinate

5.1.17. Orgain Organic Protein Powder

- Brown rice, chia, and pea proteins are among the plant sources used to make this protein powder. Stevia is used as a sweetener, and 60 milligrams of caffeine is added, which is quite moderate
- Made without artificial flavors or preservatives, dairy, gluten, lactose, or added sugar
- Each serving has two grams of dietary fiber [107]

5.2. Dosage of Supplements

A study was conducted to ascertain the ideal timing, dosages, and length of consumption for athletic dietary supplements, which were supported by scientific data demonstrating an improvement in efficiency in both training and lab environments. The results of this study explained below with some references.

A number of nutrient-dense sports meals and supplements have been shown to have a significant impact on energy supply, including creatine and carbohydrate

supplements4, as well as physiological buffering agents such sodium bicarbonate and β-alanine. This study examined the data to establish the best timing as well as dosages for sports supplements that have been shown by science to improve performance in both training and laboratory environments. B-alanine, beetroot juice (nitrate), caffeine, creatine, sodium bicarbonate, carbohydrates, as well as proteins were among these athletic supplements.

It was shown that after acute β-alanine dietary supplements, β-alanine ought to be given at a recurring dose of 1.2g. Additionally, β-alanine must be administered at an amount of 3-6 g with every snack that contains protein and carbohydrates. It is advised to consume 140 ml (8.4 mmol) of nitrate-rich beetroot juice two to three hours before engaging in intermediate range and stamina activity. 30 to 60 minutes before an exercise session, 3-6 mg/ (kg bw) of caffeine should be consumed. The ideal types of creatine to supplement with are monohydrate, which should be taken in daily doses of 3-5 g, or, for greatest absorption, 20 g split over 4 daily intakes of 5 g in addition to protein and carbohydrates.

Supplementing with carbs prior to exercising is crucial for enhancing the efficiency of exercise. 1-4 g/kg of carbohydrates are said to be required 1-4 hours prior to exercise. Furthermore, while exercise staying less than 60 minutes, carbohydrate mouthwash can enhance the effectiveness of exercise (~2-3%), mediated via receptors in the oral cavity and brain. It is advised to consume 90 g/h of mixed carbs (60 g/h of glucose plus 30 g/h of fructose) when exercising for longer than 60 minutes. This is crucial for three-hour or longer endurance events, as glycogen replenishment after exercise requires 1.2 g/kg/h of carbohydrates.

Lastly, to promote protein synthesis in the muscles, 20–25 g of protein ought to be consumed every major food, just after physical activity, and right before bed. To find out which dosage and when in the supplementing process is most important for an athlete's well-being and performance, additional research is necessary in this area. Lastly, it is advised to conduct numerous trials to assess the consistency of the efficacy benefits of supplement ingestion [108].

5.3. Interactions and Contraindications

Another article was reviewed which was studied on the purpose of to assess the known interactions among medications and contraindications for dietary supplements and herbs. Using dietary supplements and herbs (HDS) either by alone or in conjunction with prescription drugs may raise the possibility of side effects for patients.

213 dietary supplements and herbs entities and 509 drugs were involved in the 1,491 unique pairings of dietary supplements and herbs-drug interactions that were reviewed, encompassing 85 primary literatures, six books, and two websites. Dietary supplements and herbs goods with St. John's Wort, ginkgo, magnesium, calcium, iron, and other ingredients had the highest number of recorded drug interactions. Digoxin, ticlopidine, aspirin, insulin, warfarin, and aspirin had the highest quantity of HDS interaction reports. Interactions between medications and dietary supplements and herbs were well-documented when they affected the cardiovascular as well as central nervous systems. 42.3% of the 882 dietary supplements and herbs-drug encounters with their mechanism and severity being explained were related to changed pharmacokinetics, and 240 of these interactions were classified as severe ones. Out of the 152 dietary supplements and herbs contraindications that were found, neurological disorders (14.5%), gastrointestinal disorders (16.4%), and renal/genitourinary diseases (12.5%) were the most common. Of all the plants, yohimbe, echinacea, and flaxseed had the most recorded contraindications.

Distribution of drugs that may interact with nutritional supplements and plants. Anatomical therapeutic chemicals, or ATCs. There were 509 drugs in all. Drugs that have the most interactions with nutritional supplements and herbs. Herbs, dietary supplements, and HDS.

An organized synopsis of the evidence supporting the most extensively reported drug interactions and contraindications with dietary supplements and herbs is given in this review. Healthcare professionals should pay particular attention to the interactions between any dietary supplements and herbs products containing St. John's Wort, magnesium, calcium, iron, and ginkgo, and medications that affect the central nervous

system (CNS) or the cardiovascular system, even though our findings primarily concern a fairly small number of medications that are frequently prescribed and dietary supplements and herbs entities. These results need to assist medical practitioners in determining the key regions where sharing information about dietary supplements and herbs usages might most effectively avert unfavorable consequences and enhance patients' therapeutic results [109].

6. Recommendations

Every individual has their own experience with food, and this makes each of us have a unique idea of what a nutritious meal may look like. Nutrition is a subjective approach; we all need different amount of nutrients to address our health concerns. What might work for a healthy individual may not work for an individual with a metabolic disorder. Eating is an experience, pleasurable for some, and a means of warding off hunger and fuel for carrying out life activities for others. This means that, to address nutritional deficiencies, there must be a diverse approach, as one size doesn't fit all. Nutrition is far more complicated than just eating the right food and investing in the right supplements; it is also about the socioeconomic status of an individual. Not everyone has the means to afford nutritious food; some might have the power to afford but not the knowledge to access. The role of a health care provider is crucial in all these matters. It is the duty of your health care provider to rightfully determine the cause of your symptoms and to take corrective measures. They can also provide you with a list of preventive measures that can be taken to avoid deficiencies in the first place; a meal plan with supplements designed specifically keeping in mind the socioeconomic status of the patient can also be made. The definition of nutrition is far from straightforward; it is basically "the relationship between a man and the food he consumes." This definition shows a broader perspective; from the supply of food to the selection of food and till the absorption of food. Leading to the consequences of the nutrients absorbed in the body. Now that we have developed an understanding of how nutrition impacts and why regulations are important, let's see what can be done to address deficiencies.

6.1. Dietary adjustments and lifestyle changes

Lifestyle has a huge impact on health. This involves eating habits as well as daily routine of an individual. To address nutritional deficiency; key element is to focus on adjustments in lifestyle. Though, genetics play a huge role in an individual's health, often the environment, lifestyle and dietary habits outweighs the impact of genes. A greater discussion will follow in subsequent headings in this chapter.

Dietary patterns are what a person eats, frequency of the meals and common mode of preparation. Adjustments in these patterns refer to dietary adjustments. It is imperative to know that not everyone needs adjustments. Why the need of adjustment arises? It is simple because, healthy dietary patterns help eliminate or minimize health complications [110].

6.2. Maximizing nutrient intake

Start by having your caloric needs assessed and try staying above your BMR calories and within your maintenance calories. Make sure you consume balanced meal that has all major food groups. Fruits, vegetables and dairy products are good sources of water-soluble vitamins. Animal meat and cruciferous vegetables can be an excellent source of fat-soluble vitamins. Eating balanced diet will help maintain adequate amount of these and some additional nutrients in body. Unless the patient has complications in gut causing malabsorption, removed gallbladder which caused the metabolisms insufficiency of fat-soluble vitamins due to no bile acid or not eating enough nutrient dense foods. To address this, lifestyle adjustments should be made. Lifestyle includes physical activity, sleeping patterns, use of drugs and other controllable factors. Taking conscious measures in practicing healthy lifestyle can aid in living a healthy life. Following lifestyle adjustments are recommended.

6.2.1. Physical activity

In 2008, Health and Human services released physical activity guidelines, that states being physically active is one of the most important step individuals of all ages can take to live a better life. These guidelines are backed up by science-based evidence and

targets individuals from age 6 to older. The aim is to make physical activity part of daily routine. It is important to find opportunities that engage our bodies in moderate-to-vigorous physical activity. For instance, aerobic, muscle and bone strengthening exercises. Move more and sit less throughout the day. Try burning the additional calories ingested in a day. Evidence shows walking ten thousand steps a day has positive impact on insulin resistance. Physical activity has proven to be beneficial in improving cognitive health, bone health, cardiovascular health, reduced risk of fall related injuries [111] and overall enhance better nutrient metabolism by optimizing transit of food from the digestive tract to other parts of body leading to better absorption of body [102].

6.2.2. Sleep pattern

Research suggests that sleep pattern also has effect on absorption of regulating micronutrients. Optimal sleep of 6-8 hours should be consumed along with healthy diverse food choices. There has been elevation in minerals like iron, zinc and magnesium with good sleep patterns [112].

6.2.3. Drug use

It is advised to eliminate use of recreational drugs, to improve overall nutritional status. A study suggests that smoking increases bone loss and decreases intestinal absorption of calcium [113].

6.2.4. Cooking methods

Cooking methods also impacts availability of nutrients in food. Micronutrients as vitamins and minerals are subject to change in their content because of cooking method. For instance, cooking in iron utensils enriches the food with iron. On the other hand, heating causes loss of vitamin c from foods, thus prolonged cooking of vegetables can cause great loss of their vitamin c content. Stay up to date with new trends of cooking that minimizes loss of nutrients [114].

6.2.5. Dietary changes

A diversified diet is a one that includes all macro and micronutrients required for optimal health. Different types of diets also have an impact on nutritional status. For example, a vegan diet can put you at risk of vitamin B-12 deficiency. Thus, substituting with B-12 fortified foods and daily supplementation is advised.

Other changes can include mindful eating habits, avoiding processed foods, eating balanced ratio of macronutrients, supplementing with vitamins and minerals and hydration [115].

6.3. Proper use of supplements as advised

Nutritional deficiencies can have life threatening effect on health; interventions by trained professionals can aid overcoming them. This section entails how professional help can be sought to prevent deficiencies.

6.4. Role of Health Care Providers

Health care providers play pivotal role in identifying nutritional deficiencies. Several biochemical indicators (assessment of blood and urine samples for a variety of nutrients) and clinical indicators (external changes in appearance of body) can be used to identify individuals at risk of nutritional deficiencies. They can advise use of supplements accordingly.

6.5. Nutrient and drug interaction

Health care providers can identify possible drug-drug interaction or drug nutrient interaction. Patients are advised to maintain transparency and use following techniques to properly use supplements for maximal nutrient absorption. A personalized plan that has information of all the drugs patient is using and all the advised supplements along with time of intake to prevent possible interactions. For example, iron and zinc are advised to be taken at different times to avoid drug-drug interaction.

Dietary supplements are usually advised to be taken with meals to avoid GERD. All supplements should be taken with water and not any other beverage, except vitamin d

that can be taken with milk to increase absorption. Follow the dose advised by your health care provider and do not exceed the limit. Do follow up tests of clinical and biochemical indicators to see efficacy of supplement use. Inform your provider about any possible complication or issues you are experiencing. Not following recommendations can put an individual at a risk of supplement toxicity [115].

6.6. Affordability and Accessibility

Food insecurity is public health issue. Common barrier in consuming healthy diet is affordability and accessibility, influenced by socioeconomic status. Transportation of food to distant areas is also a reason for inaccessibility. Steps to overcome this span over multiple aspects like nutrition education, community nutrition, government policies and subsidies for people who face difficulty in obtaining nutritious diet. Therefore, in food insecure families all these factors play an important role in food access and availability.

This can be addressed by providing nutrition education to all. This is a government led initiative. Development and implementations of policies that subsidizes high taxes on nutritious food. Educating farmers on ways to produce more food locally and targeting accessibility. Community programs that educate local community on how they can grow fresh nutritious food and how they should address common nutritional deficiencies. Public health campaigns can also help in educating local community and can create awareness about government led programs that target food insecurities.

Supplements can be made more in reach by regulating prices and taxes. Health care provider should know different brands for a supplement to offer a range of price patient can choose from. Online platforms can also be used to market supplements. These ads reach a greater audience. Supplement manufacturers can also offer discounts and partner with local pharmacies to make supplements more affordable [116].

7. Conclusion

In this chapter, we have explored the critical issue of nutritional deficiencies and their impact on overall health and well-being. One of the key points discussed is the

importance of adopting a balanced diet and making lifestyle adjustments to effectively combat these deficiencies. A balanced diet, consisting of a variety of nutrient-rich foods, is essential for addressing nutritional deficiencies. By incorporating regular physical activity and managing stress levels, individuals can further support their overall health. Additionally, adopting appropriate dietary patterns, such as the Mediterranean or DASH diet, can help individuals maximize their nutrient intake and combat deficiencies. Emphasizing the consumption of fruits, vegetables, whole grains, lean proteins, and healthy fats can provide a wide range of essential nutrients.

In some cases, dietary supplements may be necessary to address specific nutrient deficiencies. However, it is important to consult healthcare professionals before starting any supplementation regimen to ensure appropriate dosages and avoid potential interactions with medications. Access to nutritious food can be a challenge for many individuals, particularly those in low-income communities or food deserts. Government-led initiatives and nutrition education programs are crucial in addressing these challenges and promoting access to affordable and nutritious food options.

Nutritional deficiencies can arise from various factors, including inadequate dietary intake, underlying medical conditions, and certain lifestyle choices. Identifying and addressing the root causes of deficiencies is essential for effective management. By addressing nutritional deficiencies, individuals can prevent the onset of various health conditions, such as cardiovascular diseases, diabetes, and osteoporosis. Adequate nutrient intake, particularly calcium and vitamin D, is vital for maintaining skeletal-muscular health and preventing conditions like osteoporosis. It is important to be aware of potential interactions between medications and dietary supplements. Some medications may interfere with nutrient absorption or metabolism, highlighting the need for caution and consultation with healthcare professionals.

In conclusion, addressing nutritional deficiencies through a balanced diet, lifestyle adjustments, and appropriate supplementation is crucial for maintaining optimal health. Government initiatives and nutrition education programs play a vital role in promoting access to affordable and nutritious food options. By identifying and addressing the causes of deficiencies, individuals can prevent the onset of health

conditions and improve skeletal-muscular health. It is important to be mindful of potential interactions between medications and dietary supplements and consult healthcare professionals for personalized guidance. Prioritizing nutritional needs and taking proactive steps to address deficiencies can lead to improved overall health and well-being.

Author Contributions

This chapter is the result of a collaborative effort. Each author made significant contributions to different aspects in conceptualization, research, writing, and editing.

Acknowledgments

We express our appreciation to all those who supported and contributed to this chapter. Special thanks to mentors, and colleagues that facilitated the development of this work. The guidance and feedback received played a crucial role in refining the content.

Conflicts of Interest

The authors declare no conflicts of interest. Our commitment is to present unbiased and valuable insights. Transparency is maintained to uphold the integrity of the work.

References

1. *Agha Khan University Hospital*. 2018.
2. *World Health Organization*. 2020.
3. *Benifits of Healthy Eating.* 2021.
4. Chuah, K.H., et al., *Small Intestinal Bacterial Overgrowth In Various Functional Gastrointestinal Disorders: A Case–Control Study.* 2022. **67**(8): p. 3881-3889.
5. Kiani, K.A., et al., *National Library of Medicine*. 2022.
6. Stewart, D.A., *How nutritional deficiencies Develop*.
7. Khan, Y. and Z. Bhutta, *Nutritional Deficiencies in the Developing World: Current Status and Opportunities for Intervention.* https://www.sciencedirect.com/journal/pediatric-clinics-of-north-america, 2010. **57**(6): p. 1409-1441.
8. Gillespie, S. and M.v.d. Bold, *Agriculture, Food Systems, and Nutrition: Meeting the Challenge*. 2017.
9. Kerr, M., *Malabsorption Syndrome*. 2023.
10. *Nutrient Requirements*. 2016.
11. Wiseman, M. and A.A. Jackson, *Nutrition in health and diseases* Clinical Medicine, 2004. **4**(5): p. 397-400.
12. *15 Medical Conditions that make it tough to eat*. 2022.
13. Hagve, M., et al., *Nutritional support for critically ill patients in the intensive care unit*. 2020.
14. Rice, S.C., *Nutrition and Metabolism Disorders*. 2018.
15. *How Diet Impacts Bone Health*. 2019.
16. Dunphy, M., *Muskuloskeletal Health*. 2016.
17. Firth, J., et al., *Food and mood: how do diet and nutrition affect mental wellbeing?* 2020.
18. Spencer, S.J., et al., *Food for thought: how nutrition impacts cognition and emotion*. 2017.
19. I., J., *The Connection Between Nutrition and Mental Health*. 2021.
20. Renzo, L.D., P. Gualiteri, and A. De Lorenzo, *Diet, Nutrition and Chronic Degenerative Diseases*. 2013.
21. Graber, E., *Nutrition and Chronic Disease*. 2022.
22. Suskind, D.L., *Nutritional Deficiencies During Normal Growth*. 2009.
23. Sommer, A. and K.P. West, *Vitamin A deficiency: health, survival, and vision*. 1996: Oxford University Press.
24. Sherwin, J.C., et al., *Epidemiology of vitamin A deficiency and xerophthalmia in at-risk populations.* Trans R Soc Trop Med Hyg, 2012. **106**(4): p. 205-14.
25. Langan, R.C. and A.J. Goodbred, *Vitamin B12 Deficiency: Recognition and Management.* Am Fam Physician, 2017. **96**(6): p. 384-389.
26. Oh, R. and D.L. Brown, *Vitamin B12 deficiency.* Am Fam Physician, 2003. **67**(5): p. 979-86.
27. Shipton, M.J. and J. Thachil, *Vitamin B12 deficiency - A 21st century perspective* Clin Med (Lond), 2015. **15**(2): p. 145-50.
28. Fain, O., *[Vitamin C deficiency].* Rev Med Interne, 2004. **25**(12): p. 872-80.
29. health, n.i.o., *Fact Sheet for vitamin C.* March 26, 2021.
30. Carr, A.C. and S. Maggini, *Vitamin C and Immune Function.* Nutrients, 2017. **9**(11).
31. Health, N.I.o., *Dietary Reference Intakes for Calcium and Vitamin D.* 2011.
32. Prentice, A., *Vitamin D deficiency: a global perspective.* Nutrition Reviews, 2008. **66**(suppl_2): p. S153-S164.
33. Lobo, L.M.C. and M. Hadler, *Vitamin E deficiency in childhood: a narrative review.* Nutr Res Rev, 2023. **36**(2): p. 392-405.
34. Di Donato, I., S. Bianchi, and A. Federico, *Ataxia with vitamin E deficiency: update of molecular diagnosis.* Neurological sciences, 2010. **31**: p. 511-515.

35. Marchili, M.R., et al., *Vitamin K deficiency: a case report and review of current guidelines.* Ital J Pediatr, 2018. **44**(1): p. 36.
36. Mihatsch, W.A., et al., *Prevention of Vitamin K Deficiency Bleeding in Newborn Infants: A Position Paper by the ESPGHAN Committee on Nutrition.* J Pediatr Gastroenterol Nutr, 2016. **63**(1): p. 123-9.
37. Weininger, J., *Nutritional Disease.* Oct 27, 2023.
38. Tulchinsky, T.H., *Micronutrient deficiency conditions: global health issues.* Public health reviews, 2010. **32**: p. 243-255.
39. Al-Ghamdi, S.M., E.C. Cameron, and R.A. Sutton, *Magnesium deficiency: pathophysiologic and clinical overview.* American Journal of Kidney Diseases, 1994. **24**(5): p. 737-752.
40. Serefko, A., A. Szopa, and E. Poleszak, *Magnesium and depression.* Magnes Res, 2016. **29**(3): p. 112-119.
41. Tuerk, M.J. and N. Fazel, *Zinc deficiency.* Current opinion in gastroenterology, 2009. **25**(2): p. 136-143.
42. Zimmermann, M.B., *Iodine deficiency.* Endocr Rev, 2009. **30**(4): p. 376-408.
43. Patrick, L., *Iodine: deficiency and therapeutic considerations.* Alternative Medicine Review, 2008. **13**(2).
44. Ifwat, A., et al., *Xerophthalmia in Picky Eater Children.* Cureus, 2022. **14**(3).
45. Aşkın, Ö., et al., *Vitamin deficiencies/hypervitaminosis and the skin.* Clinics in Dermatology, 2021. **39**(5): p. 847-857.
46. Zinder, R., et al., *Vitamin A and wound healing.* Nutrition in Clinical Practice, 2019. **34**(6): p. 839-849.
47. Charoenngam, N., A. Shirvani, and M.F. Holick, *Vitamin D for skeletal and non-skeletal health: What we should know.* Journal of clinical orthopaedics and trauma, 2019. **10**(6): p. 1082-1093.
48. Hyppönen, E., et al., *Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study.* The Lancet, 2001. **358**(9292): p. 1500-1503.
49. Dayel, S.B. and R.S. Hussein, *Vitamin Deficiencies and Their Impact on Skin Function.*
50. Ogeyingbo, O.D., et al., *The relationship between vitamin D and asthma exacerbation.* Cureus, 2021. **13**(8).
51. Fazelian, S., et al., *Effect of vitamin D supplement on mood status and inflammation in vitamin D deficient type 2 diabetic women with anxiety: a randomized clinical trial.* International journal of preventive medicine, 2019. **10**.
52. Kim, S.-Y., et al., *Vitamin D deficiency and suicidal ideation: A cross-sectional study of 157,211 healthy adults.* Journal of psychosomatic research, 2020. **134**: p. 110125.
53. Ismailova, A. and J.H. White, *Vitamin D, infections and immunity.* Reviews in Endocrine and Metabolic Disorders, 2022: p. 1-13.
54. DiBaise, M. and S.M. Tarleton, *Hair, nails, and skin: differentiating cutaneous manifestations of micronutrient deficiency.* Nutrition in Clinical Practice, 2019. **34**(4): p. 490-503.
55. Kemnic, T.R. and M. Coleman, *Vitamin E deficiency*, in *StatPearls [Internet]*. 2023, StatPearls Publishing.
56. Sherry, K. and B. Gallagher, *Coagulation testing: what to do and how to do it.* In Practice, 2022. **44**(5): p. 270-283.
57. Zekavat, O.R., et al., *Acquired vitamin K deficiency as unusual cause of bleeding tendency in adults: A case report of a nonhospitalized student presenting with severe menorrhagia.* Case Reports in Obstetrics and Gynecology, 2017. **2017**.
58. Wiley, K.D. and M. Gupta, *Vitamin B1 thiamine deficiency.* 2019.
59. Mahabadi, N., A. Bhusal, and S.W. Banks, *Riboflavin deficiency*, in *StatPearls [Internet]*. 2022, StatPearls Publishing.
60. Redzic, S. and V. Gupta, *Niacin deficiency.* 2020.

61. Sanvictores, T. and S. Chauhan, *Vitamin B5 (pantothenic acid)*. 2020.
62. Saleem, F. and M.P. Soos, *Biotin deficiency*. 2019.
63. Khan, K.M. and I. Jialal, *Folic acid deficiency*. 2018.
64. Sijilmassi, O., *Folic acid deficiency and vision: a review*. Graefe's Archive for Clinical and Experimental Ophthalmology, 2019. **257**(8): p. 1573-1580.
65. Schafer, A.L. and D.M. Shoback, *Hypocalcemia: diagnosis and treatment*. 2015.
66. Goyal, A., et al., *Hypocalcemia*. 2017.
67. Capozzi, A., G. Scambia, and S. Lello, *Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health*. Maturitas, 2020. **140**: p. 55-63.
68. Intakes, I.o.M.S.C.o.t.S.E.o.D.R., *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. 1997.
69. Eastman, C.J. and M.B. Zimmermann, *The iodine deficiency disorders*. 2015.
70. Wołoszynowska-Fraser, M.U., A. Kouchmeshky, and P. McCaffery, *Vitamin A and retinoic acid in cognition and cognitive disease*. Annual review of nutrition, 2020. **40**: p. 247-272.
71. Ramsey, D. and P.R. Muskin, *Vitamin deficiencies and mental health: How are they linked*. Current Psychiatry, 2013. **12**(1): p. 37-43.
72. Soni, M., et al., *Vitamin D and cognitive function*. Scandinavian Journal of Clinical and Laboratory Investigation, 2012. **72**(sup243): p. 79-82.
73. Lerner, P.P., L. Sharony, and C. Miodownik, *Association between mental disorders, cognitive disturbances and vitamin D serum level: Current state*. Clinical nutrition ESPEN, 2018. **23**: p. 89-102.
74. Guo, M., et al., *Vitamin A and vitamin D deficiencies exacerbate symptoms in children with autism spectrum disorders*. Nutritional neuroscience, 2019. **22**(9): p. 637-647.
75. Huskisson, E., S. Maggini, and M. Ruf, *The influence of micronutrients on cognitive function and performance*. Journal of international medical research, 2007. **35**(1): p. 1-19.
76. Malouf, R., et al., *Vitamin B6 for cognition*. Cochrane Database of Systematic Reviews, 1996. **2010**(1).
77. Muscaritoli, M., *The impact of nutrients on mental health and well-being: insights from the literature*. Frontiers in nutrition, 2021: p. 97.
78. Atmaca, M., et al., *Serum folate and homocysteine levels in patients with obsessive-compulsive disorder*. Psychiatry and clinical neurosciences, 2005. **59**(5): p. 616-620.
79. Ulatowski, L.M. and D. Manor, *Vitamin E and neurodegeneration*. Neurobiology of disease, 2015. **84**: p. 78-83.
80. Browne, D., et al., *Vitamin E and Alzheimer's disease: what do we know so far?* Clinical interventions in aging, 2019: p. 1303-1317.
81. Tanyel, M. and L. Mancano, *Neurologic findings in vitamin E deficiency*. American family physician, 1997. **55**(1): p. 197-201.
82. Jáuregui-Lobera, I., *Iron deficiency and cognitive functions*. Neuropsychiatric disease and treatment, 2014: p. 2087-2095.
83. Kirkland, A.E., G.L. Sarlo, and K.F. Holton, *The role of magnesium in neurological disorders*. Nutrients, 2018. **10**(6): p. 730.
84. Pop, O.L., et al. *Micronutrients Deficiencies in Early Life and Impact on Long-term Health*. 2020.
85. Smith, J. and T.L. Steinemann, *Vitamin A deficiency and the eye*. International ophthalmology clinics, 2000. **40**(4): p. 83-91.
86. Black, M.M., *Micronutrient deficiencies and cognitive functioning*. The Journal of nutrition, 2003. **133**(11): p. 3927S-3931S.
87. Stevens, G.A., et al., *Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys*. The Lancet Global Health, 2022. **10**(11): p. e1590-e1599.

88. Kodama, H., *Trace element deficiency in infants and children.* JMAJ, 2004. **47**(8): p. 376-81.
89. Carpenter, T.O., et al., *Rickets.* Nature Reviews Disease Primers, 2017. **3**(1): p. 1-20.
90. Rogol, A.D., *Causes of short stature.* UpToDate online, 2019. **14**.
91. Rees, L., *Protein energy wasting; what is it and what can we do to prevent it?* Pediatric Nephrology, 2021. **36**(2): p. 287-294.
92. Thacher, T.D., et al., *Nutritional rickets around the world: causes and future directions.* Annals of tropical paediatrics, 2006. **26**(1): p. 1-16.
93. Bhadra, P. and A. Deb, *A review on nutritional anemia.* Indian Journal of Natural Sciences, 2020. **10**(59): p. 18466-18474.
94. Xing, M., et al., *Low iodine intake may decrease women's fecundity: A population-based cross-sectional study.* Nutrients, 2021. **13**(9): p. 3056.
95. Aoun, A., V. El Khoury, and R. Malakieh, *Can Nutrition Help in the Treatment of Infertility?* Preventive nutrition and food science, 2021. **26**(2): p. 109.
96. Hejazi, J., et al., *Nutrition and osteoporosis prevention and treatment.* Biomedical Research and Therapy, 2020. **7**(4): p. 3709-3720.
97. Szczechowiak, K., B.S. Diniz, and J. Leszek, *Diet and Alzheimer's dementia–Nutritional approach to modulate inflammation.* Pharmacology Biochemistry and Behavior, 2019. **184**: p. 172743.
98. Serhan, H.A., et al., *Ophthalmic manifestations of nutritional deficiencies: A mini review.* Journal of Family Medicine and Primary Care, 2022. **11**(10): p. 5899-5901.
99. Musa, M., et al., *Nutritional Factors: Benefits in Glaucoma and Ophthalmologic Pathologies.* Life, 2023. **13**(5): p. 1120.
100. Olson, J.M., M.A. Ameer, and A. Goyal, *Vitamin A toxicity.* 2018.
101. Asif, A. and N. Farooq, *Vitamin D toxicity*, in *StatPearls [Internet]*. 2023, StatPearls Publishing.
102. Owen, K.N. and O. Dewald, *Vitamin E toxicity.* 2020.
103. Krupa, K., K. Fritz, and M. Parmar, *Omega-3 fatty acids.* 2020.
104. Suppliments, N.I.o.H.O.o.D., *Dietary Supplement Fact Sheets* https://ods.od.nih.gov/factsheets/list-all/. 2023.
105. *FDA 101: Dietary Supplements*, in *U.S. Food & Drug*. 06.
106. Khattak, R., *FOOD AND DIETARY SUPPLEMENTS: The Unregulated Industry of Food Supplements in Pakistan*, in *Research Gate*. 2022.
107. Sarah Davis, V.W., *7 Best Probiotic Supplements Of 2023, According to Experts*, in *Forbes Health*. 2023.
108. Alireza Naderi, E.P.d.O., Tim N. Ziegenfuss, and Mark E.T. Willems, *Timing, optimal dose and intake duration of dietary supplements with evidence-based use in sports nutrition*, in *National Library of Medicine*. 2016.
109. H.-H. Tsai, H.-W.L., A. Simon Pickard, H.-Y. Tsai, G. B. Mahady, *Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review*, in *Wiley Online Library*. 2012.
110. Barasi, M.E., *HUMAN NUTRITION*

A health perspective. 2003, Great Britian. 416.
111. Prevention, C.f.D.C.a. *Benefits of Physical Activity*. 2023; Available from: https://www.cdc.gov/physicalactivity/basics/pa-health/index.htm.
112. Al-Bashaireh, A.M., et al., *The effect of tobacco smoking on bone mass: an overview of pathophysiologic mechanisms.* Journal of osteoporosis, 2018. **2018**.
113. Ji, X., M.A. Grandner, and J. Liu, *The relationship between micronutrient status and sleep patterns: a systematic review.* Public health nutrition, 2017. **20**(4): p. 687-701.

114. Tyagi, S., M. Kharkwal, and T. Saxena, *Impact of cooking on nutritional content of food.* DU Journal of Undergraduate Research and Innovation, 2015. **1**(3): p. 180-186.
115. Niklewicz, A., et al., *The importance of vitamin B12 for individuals choosing plant-based diets.* European Journal of Nutrition, 2023. **62**(3): p. 1551-1559.
116. Ziso, D., O.K. Chun, and M.J. Puglisi, *Increasing Access to Healthy Foods through Improving Food Environment: A Review of Mixed Methods Intervention Studies with Residents of Low-Income Communities.* Nutrients, 2022. **14**(11): p. 2278.